Thomas A. Waldmann, M.D.
Chief of the Metabolism Branch and the Waldmann Laboratory
Building 10
Room 4N117
Phone 301-496-6653
Fax 301-496-9956
E-mail tawald@helix.nih.gov

Biography - Dr. Waldmann
Recent Publications
Collaborators
Clinical Trials

Metabolism Branch

The IL-2/IL-15 Receptor System: A Target for Cancer Therapy

Keywords

- lymphokines
- receptors
- immunotherapy
- acute (adult) T cell lymphoma/leukemia

Our work on basic and clinical immunology focuses on the regulation of the human immune response and how its disregulation can lead to autoimmune, immunodeficiency, and malignant disorders. We apply insights gained in fundamental research to the development of new approaches to the treatment of patients. Our recent studies focus on the critical role played by the receptor for interleukin-2 (IL-2) on the growth and differentiation of normal and neoplastic T cells. Resting cells do not express high affinity IL-2 receptors (IL-2R), but receptors are rapidly expressed on T cells after activation. We defined two of the IL-2R subunits, IL-2R(alpha) and IL-2R(beta), that together with IL-2R(gamma) are participants in the high affinity form of the receptor. As part of our study of HTLV-I-associated adult T cell leukemia (ATL), we codiscovered the cytokine IL-15 that stimulates T cell proliferation and NK cell development. There is widespread expression of IL-15 mRNA in a variety of tissues and cells. Nevertheless, it is difficult to demonstrate meaningful quantities of IL-15 in the supernatants of these message-expressing cells, suggesting that there are critical posttranscriptional regulatory events affecting IL-15 expression. The IL-15 message includes a number of elements that are impediments to its translation. In particular, the 5' UTR of normal human IL-15 message is burdened with 10 upstream AUG's that interfere with efficient IL-15 translation. Furthermore, the unusually long 48 aa leader sequence interferes with this process. As a hypothesis, we propose that by maintaining a pool of translationally inactive IL-15 mRNA, cells can readily respond to an intracellular infection by unburdening the IL-15 message, transforming it into one that can be effectively translated.

For its action in T cells, IL-15 utilizes a multisubunit receptor that includes a specific IL-15Ra receptor element as well as two receptor subunits, IL-2R(beta) and the common gamma (gc) chain shared with the IL-2R. gc and its proximal signal transduction element JAK-3 are not only required for the actions of IL-2 and IL-15 but

are also used by IL-4, IL-7, and IL-9. A major corollary of this sharing of cytokine receptor subunits is that therapy directed toward a shared cytokine receptor (e.g., IL-2R(beta) or (gamma)c) or shared membrane proximal transduction element (e.g., JAK-3) may yield more profound immunosuppression than can be achieved by the inhibition of a single cytokine (IL-2). Recently our group defined a second IL-15-specific receptor and signaling pathway in mast cells. In such cells we demonstrated that IL15 binding and signaling involves a receptor system that does not share any subunits with the IL-2R system. Rather it utilizes a novel receptor IL-15RX. Furthermore, this novel IL-15R system employs a signal transduction pathway involving JAK-2 and STAT-5 that is distinct from the JAK-1/3 and STAT-3/5 used by the IL-2/IL-15R system in T cells.

One of our most crucial contributions was the recognition that the IL2R represents an extraordinarily useful therapeutic target. The scientific basis for this approach is that resting cells do not express IL2Ra whereas this receptor subunit is abundantly expressed by a variety of malignant cells including the leukemic cells in adult T cell leukemia. In a clinical trial involving 90Y-anti-Tac (anti-IL-2R(alpha)) therapy for patients with HTLV-I-associated ATL, we observed a partial or complete remission in over 50 percent of patients. Recently we extended these studies by initiating new clinical trials using 90Y-linked to humanized rather than murine anti-Tac to provide a relatively nonimmunogenic agent for treatment of an extended array of human leukemias and lymphomas. New agents under active development include humanized antibodies directed toward private and shared cytokine receptors (e.g., IL-2R(beta)) armed with a-emitting radionuclides (212Bi, 213Bi, 211At) as well as small molecular agents that inhibit the tyrosine kinase JAK-3 that is required for IL-2, IL-4, IL-7, IL-9, and IL-15 action. Thus, new insights concerning receptors and signaling pathways used by malignant cells taken in conjunction with the ability to produce humanized antibodies armed with radionuclides are providing a novel perspective for the treatment of select neoplastic diseases.

Recent Publications

Bamford, R, et al. Proc Natl Acad Sci USA 1996; 93:2897-902.
Tagaya, Y, et al. Immunity 1996; 4:329-36.
Tagaya, Y, et al. EMBO J 1996; 15:4928-39.
Waldmann, T, et al. Blood 1995; 86:4063-75.

Collaborators

Martin Brechbiel, Ph.D.; Jorge Carrasquillo, M.D.; William Eckelman, Ph.D.; Steven Jacobson, Ph.D.; Robert Kreitman, M.D.; Henry McFarland, M.D.; Robert Nussenblatt, M.D.; and Ira Pastan,

M.D., NIH
John Hakimi, Ph.D., Hoffmann-La Roche, Inc.
Wayne Marasco, M.D., Ph.D., Dana-Farber Cancer Institute
Gillian Wharfe, M.D., University of the West Indies

Clinical Trials

77-C-0066
Waldmann, et al. Studies of the immune response in normal subjects and patients with disorders of the immune system. These studies led and continue to lead to the discovery of new immunodeficiency diseases and previously undefined pathogenic mechanisms leading to immunodeficiency including those associated with cancer, and to the demonstration that human T cell leukemias may retain helper, suppressor, and suppressor-activator activity, providing new insights concerning the network of cells controlling the immune response.

82-C-0044
Nelson, et al. Investigation of human in vitro cellular immune response

83-C-0023
Waldmann, et al. Preliminary feasibility study of monoclonal anti-Tac antibody immunotherapy of adult T cell leukemia (ATL). In this trial, we demonstrated that therapy with a murine antibody to the IL-2R(alpha) (anti-Tac) is associated with remissions in a proportion of patients with ATL without associated toxicity.

93-C-0066
Waldmann, et al. Treatment of Tac-expressing adult T cell leukemia with yttrium-90 labeled humanized anti-Tac monoclonal antibody. We demonstrated that arming of the anti-Tac monoclonal antibody with the (beta)-emitting radionuclide 90Y increases its efficacy in the therapy of IL-2Ra(alpha)-expressing ATL. Furthermore, the use of a humanized version of the Mab in lieu of murine anti-Tac reduces its immunogenicity.

94-C-0068
Treatment of Tac-expressing postthymic T cell malignancies (other than adult T cell leukemia [ATL]) with yttrium-90 humanized anti-Tac. This expands the types of leukemia that are being evaluated for their response to yttrium-90 anti-Tac therapy.

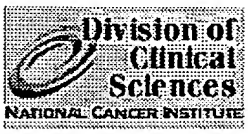
94-C-0070
White, et al. Treatment of HTLV-I-associated adult T cell leukemia (ATL) with a combination of INF alpha-2b and AZT (zidovudine)

95-C-0054

White, et al. A phase I study of T cell large granular lymphocytic leukemia using the Mikb1 monoclonal antibody directed toward the IL-2R(beta) subunit. This is the first clinical trial employing an antibody to the IL-2R(beta) subunit. In contrast to antibodies to IL-2R(alpha) (e.g., anti-Tac), this antibody blocks the action of IL-15 and inhibits IL-2 function in large granular lymphocytes that express IL-2R(beat) and (gammac but not IL-2R(alpha).

96-C-0147

Waldmann, et al. A phase I/II study of Tac-expressing adult T cell leukemia (ATL) with yttrium-90 (90Y)-labeled humanized anti-Tac monoclonal antibody and calcium-DTPA. Ca-DTPA administration facilitates yttrium-90 excretion, thereby permitting a higher dose of 90Y-anti-Tac with acceptable toxicity.



Search

Metabolism Branch Overview

Investigators and Research

Clinical Programs

Professional Opportunities

National Institutes of Health Home Page

National Cancer Institute Home Page

Division of Clinical Sciences, NCI, Home Page

Metabolism Branch
Clinical Programs

Radioimmunotherapy & Immunotherapy Program

(Jeffrey White, M.D.)
The Clinical Trials Group of the Metabolism Branch has been involved in the development of IL-2R directed therapies including use of humanized antibodies conjugated to Yttrium-90, a pure beta emitter, for therapy of IL-2R-alpha-expressing leukemias. Agents under development include humanized antibodies directed toward the cytokine receptors shared by IL-2 and IL-15, as well as antibodies armed with alpha-emitting radionuclides.

Physician referrals are necessary for admission to protocols. Information on any of the protocols listed below, which are actively recruiting patients, may be obtained from Dr. Jeffrey White by e-mail jdwhite@helix.nih.gov or by telephone 301-402-2912.

96-C-0147 *Thomas Waldmann, PI*
Phase I/II Study of Tac expressing Adult-T-Cell Leukemia(ATL) with Yttrium-90 labeled humanized anti-Tac monoclonal antibody and calcium-DTPA. We demonstrated that arming of the anti-Tac monoclonal antibody with the beta-emitting radionuclide Yttrium-90 increases its efficacy in the therapy of IL-2R alpha-expressing ATL. Use of a humanized version of the monoclonal antibody in lieu of murine anti-Tac reduces its immunogenicity, and Ca-DTPA administration facilitates Yttrium-90 excretion, thereby permitting a higher dose of Yttrium-90-anti-Tac with acceptable toxicity.

97-C-0110 *Jeffrey White, PI*
Phase I/II study of Tac-expressing malignancies{other that Adult T-cell Leukemia[ATL]}with Yttrium-90 radiolabeled humanized anti-Tac monoclonal antibody and calcium-DTPA.

95-C-0054 *Jeffrey White, PI, Thomas Waldmann, Study Chair*
Phase I Study of T-cell Large Granular Lymphocytic Leukemia using the Mik-beta-1 monoclonal antibody directed toward the IL-2R beta subunit.

This is the first clinical trial employing an antibody to the IL-2R beta subunit. In contrast to antibodies to IL-2R alpha[e.g., anti-Tac], this antibody blocks the action of IL-15 and inhibits IL-2 function in large granular lymphocytes that express IL-2R beta chain and the common gamma chain, but not IL-2R alpha.

Cancer Vaccine Program
Physicians wishing to inquire about protocol requirements for the following protocol should contact Margaret Edison of the NCI at 301-496-0905, or Peggy Krozely at Vanderbilt Medical Center, 615-343-0798

94-C-0031 *Jay A. Berzofsky, PI*
Detection of Immunologic Response and Vaccination against Tumor-Specific Mutant ras and p53 peptides in patients with cancer Translation of research approach using mutant ras and p53 peptides as tumor antigens for the immunotherapy of cancer.

Human Immunity and Immunodeficiency Program

Protocol 97-C-0143 *David Nelson, M.D., PI*
Investigation of the Human Immuune Response in Normal Subjects and Patients with Disorders of the Immune System and Cancer.

Dr. Nelson is interested in studying the immune response in normal individuals and abnormalities of these responses in patients with the Wiskott-Aldrich Syndrome, ataxia-telangiectasia, X-linked agammaglobulinemia, X-linked hyper IgM syndrome, severe combined immunodeficiency, X-linked agammaglobulinemia with isolated growth hormone deficiency, and primary and secondary immunodeficiencies of uncertain etiology.

Physician inquiries can be directed to Dr. Nelson at 301-496-3024 or by e-mail dln@helix.nih.gov

Last updated: February 02, 1999 at 15:27